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ORIGINAL INVESTIGATION

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Effects of pergolide on intravenous cocaine self-administration in men and women

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Abstract Clinical evidence suggests that pergolide, a D_1/D_2 dopamine receptor agonist, may be useful in maintaining cocaine abstinence. We investigated pergolide's effects in a laboratory model of IV cocaine self-administration by humans. Twelve inpatient volunteers (7M, 5F), who reported spending an average of $170/week on cocaine, received pergolide (0.05 mg BID) for 8 days and placebo for 8 days, with drug order balanced across subjects. Self-administration sessions occurred on the last 4 days of maintenance on each medication. A modified seven-trial progressive ratio choice procedure (0, 8, 16, 32 mg/70 kg cocaine versus $5) was utilized, with sessions consisting of: (a) two sample trials, where participants responded to receive the dose and tokens available that day, and (b) five choice trials, where participants chose between the available dose and tokens. Following each trial, the response requirement for the chosen option increased by 400. Maintenance on pergolide 1) decreased cocaine-induced increases in ratings of "High," "Stimulated," cocaine "Potency," estimates of street value, and heart rate, 2) increased ratings of "I want cocaine," and 3) had no effect on cocaine self-administration. The increased desire to use cocaine during pergolide maintenance suggests that it has limited treatment utility at this dose, but given the attenuation of cocaine's subjective and cardiovascular effects, an investigation of a wider range of pergolide doses on cocaine self-administration and subjective effects is warranted.

Key words Cocaine · Human · Self-administration · Pergolide · Sex differences · Subjective effects · Performance · Cardiovascular effects

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Introduction

Although the occasional use of cocaine has decreased in recent years, rates of cocaine abuse and dependence have remained unchanged (National Drug Control Strategy 1997). In most major US cities, cocaine abusers account for the largest proportion of admissions for drug treatment, with the exception of alcohol. Despite recent advancements in behavioral treatment for cocaine abuse (Higgins et al. 1991), there remains a clear need for effective pharmacotherapy to facilitate treatment for cocaine abuse, by maintaining people in treatment longer, and by prolonging the intervals between relapse.

Investigations of potential pharmacotherapies for cocaine abuse have included direct or indirect dopamine agonists, since cocaine's reinforcing effects are at least partly mediated by inhibition of dopamine re-uptake (Fibiger 1978; Wise and Bozarth 1987), leading to stimulation of the D_1 and D_2 families of dopamine receptors (Kebabian and Calne 1979). As of yet, the medications that have been tested have shown little promise. The indirect dopamine agonist, amantadine, did not affect cocaine "craving," treatment retention or the number of positive cocaine urines of outpatient treatment-seekers (Gawin et al. 1989; Handelsman et al. 1995; Kampman et al. 1996). Although initial reports suggested that the D_2 receptor agonist, bromocriptine, decreased cocaine craving and relieved depression in individuals seeking treatment (Dackis and Gold 1985), more recent data demonstrate that bromocriptine fails to block the subjective and physiological effects of either cocaine (Preston et al. 1992; Tennant and Sagherian 1987) or cocaine-related cues (Kranzler and Bauer 1992). Bromocriptine also produces side effects, such as nausea and fainting, which often preclude its clinical use (see Kleber 1995).

Clinical evidence suggests that the D_1/D_2 dopamine receptor agonist, pergolide mesylate, currently used

to treat Parkinson's disease (Wachtel 1991), may be an efficacious treatment medication for cocaine abuse. In a preliminary open-label study, both inpatients and outpatients reported improvement in cocaine abstinence symptomatology within 24 h of initiating treatment with pergolide (Malcolm et al. 1991). Some of the improvements included decreased cravings for cocaine, improved sleep, and better concentration. In a subsequent 30-day inpatient, randomized, open-label study, pergolide appeared to be more effective than bromocriptine, in terms of increased length of hospital stay and reduced premature discharges (Malcolm et al. 1994). Pergolide, which is 10–100 times more potent and longer-lasting than bromocriptine (Factor et al. 1988; Wachtel 1991), also produced fewer side effects. In another study investigating pergolide as a treatment for obsessive compulsive disorder and bipolar illness, the authors noted that patients spontaneously reported reductions in drug craving and the use of cocaine and alcohol (Lipinski, personal communication). Doses of pergolide that were associated with reductions in drug use and craving are far lower (0.10–0.25 mg/day) than those required to treat Parkinson's disease (3.0 mg/day).

Given these preliminary results, pergolide's effects on cocaine self-administration by humans were examined, using a procedure that mimics a bout of repeated cocaine use (Fischman et al. 1990). In this model, individuals who regularly use cocaine but who are not seeking treatment, are given the opportunity to repeatedly self-administer cocaine over several hours a day, under careful medical observation. Thus, the effects of pergolide on both the initiation and the maintenance of a cocaine "binge" could be compared to placebo conditions. Second, alternatives to drug-taking are available, just as they are outside of the laboratory. Volunteers have an "either/or" decision between access to cocaine or to tokens exchangeable for $5.00. Providing a non-drug alternative reinforcer allows us to measure the selectivity of pergolide's effects on cocaine's reinforcing efficacy. Previous studies have demonstrated that this procedure is sensitive to cocaine dose, with token choice decreasing when the corresponding cocaine dose is increased (Foltin and Fischman 1994).

The objective of this study was to determine how pergolide influences a range of measures, including cocaine self-administration, cocaine "craving," subjective-effects ratings, cardiovascular effects, and psychomotor task performance in cocaine abusers. Further, given that sex differences in the effects of cocaine have been observed in both laboratory animal (Roberts et al. 1989; Haney et al. 1994) and human studies (Lexau et al. 1995; Dudish et al. 1996; Kosten et al., 1996; Lukas et al. 1996), an additional objective was to obtain preliminary data comparing the effects of IV cocaine in men and women.

Materials and methods

Participants

Five female and seven male research volunteers (seven African-American, three Hispanic, two Caucasian), 30–45 years of age (mean ± SD; men: 37.3 + 5.2, women: 38.8 ± 2.8), with histories of IV and/or smoked cocaine use were solicited through word-of-mouth referral and newspaper advertisement in New York, NY. Participants had an average of 13 years of education. They reported currently spending $170.00 per week on cocaine (men: 179.3 ± 78.5, women: 157.0 ± 86.4), and using cocaine for the past 10.9 years (men: 8.0 ± 5.4, women: 13.8 ± 8.8). Three women and five men reported drinking alcohol weekly (men: 5.6 ± 2.3, women: 12.7 ± 6.3 drinks/week). The ten participants who smoked cigarettes were permitted to smoke ad libitum, except during laboratory sessions. Two women and two men primarily used cocaine by the IV route, while the remaining participants preferred the smoked route of cocaine administration. Five participants reported previous heroin use but none were opiate-dependent. All participants passed medical and psychological evaluation prior to the study, and none were receiving psychiatric treatment. Plasma cholinesterase values were obtained as part of the medical screening. Women were given a serum pregnancy test at screening, and a urine pregnancy test before their first overnight stay in the laboratory. None were taking oral contraceptives. Phases of the menstrual cycle were not documented in these women (Lukas et al. 1996). Each participant signed a consent form, approved by the Institutional Review Boards of The College of Physicians and Surgeons of Columbia University and The New York State Psychiatric Institute. The consent form described the study, outlined any possible risks, indicated that participants would be maintained on a potential treatment medication, and that cocaine would be administered, possibly on a daily basis. One additional female participant completed the protocol, but her data were not included in the analysis: prior to the first cocaine self-administration session, she told a nurse that she was interested in purchasing a couch and would therefore always choose tokens over cocaine, which she did.

Apparatus

During experimental sessions, each subject was seated in a comfortable lounge chair in front of a computer monitor. A computer mouse was used for completion of subjective-effects questionnaires. For blood withdrawal, an 18-gauge catheter (Quik-Cath, Travenol Laboratories, Deerfield, Ill., USA) was inserted in a subcutaneous vein on one arm; a second catheter was inserted in the other arm for drug injection. The IV lines were kept patent by a physiological saline solution drip at a rate of 2 cc/min. Electrocardiograms (ECG) were continuously monitored via chest electrodes (MAC PC, Marquette Electronics, Milwaukee, Wisc., USA) while heart rate (HR) and blood pressure (systolic; SP, diastolic; DP) were recorded every 2 min (Sentry II, Model 6100 automated vital signs monitor, NBS Medical, Costa Mesa, Calif., USA) beginning 20 min prior to drug administration. An Apple GS computer located in an adjacent room was used for automated data collection.

Procedure

Participants resided on the Irving Center for Clinical Research in The Presbyterian Hospital for the duration of the 18-day study. They had access to television, radio, and video-taped movies in their hospital rooms, and were free to smoke cigarettes in their rooms at any time. Visitors were prohibited. Participants were admitted on Wednesday, and began active or placebo maintenance medication the following day. They were trained on the computer tasks

on Thursday and Friday and began cocaine self-administration sessions the following Monday. There were a total of eight self-administration sessions in the study. Participants received oral pergolide (0.05 mg BID) for 8 days and placebo for 8 days; pergolide was administered during the first half of the study for half the participants, and during the last half of the study for the other half of participants. Pergolide or placebo was administered 4 days before cocaine was available, and there was a 4-day period between the last pergolide administration and the first cocaine self-administration session under placebo maintenance. Four doses of cocaine were tested (0, 8, 16, 32 mg/70 kg), with each dose tested for 1 day under each maintenance condition. The order of dosing was randomized, except that for safety reasons, a low dose of cocaine was tested before the highest dose of cocaine.

A choice procedure similar to that described by Fischman et al. (1990) was used during experimental test sessions. Participants were repeatedly given a choice between cocaine and a token, exchangeable for $5.00, payable upon discharge. Sessions consisted of two sample trials, where participants responded on a keyboard on a fixed ratio schedule (FR200) to receive the dose and tokens available that day, followed by five choice trials, where participants chose between the available dose and tokens. Each trial was indicated by a visual cue (two squares: 3 cm × 3 cm) on the computer screen. Participants selected the left or right option with their computer mouse (illuminating the square associated with that position), and pressed the spacebar or enter key on their computer keyboard until they completed the response requirement and the message "Left (or Right) Option Chosen" appeared at the bottom of the screen. During each session, one cue was associated with cocaine and the other with tokens. The first stimulus cue the participant selected during the sample trial was considered the cue associated with cocaine for the session. This ensured that the blood sample and behavioral measures always occurred at the same time after the sample cocaine dose. During each of the five choice trials, participants could choose to receive the cocaine dose again, or another $5.00. Following each choice, the response requirement for the chosen option increased by 400, while the response requirement for the non-chosen option did not change. Thus, if a participant chose only cocaine, the response requirements would be 600, 1000, 1400, 1800, and 2200. Choices and/or dosings occurred at 20-min intervals. Blood for determination of cocaine plasma level was drawn after the second and the last options were delivered. The session ended 30 min after the last option delivery.

During laboratory sessions, participants were continuously monitored via a one-way mirror by research nurses located in the adjacent room, and could communicate via an intercom system. Neither cocaine or tokens were given on any trial where cardiovascular activity was above the criteria for safe drug administration (HR > 130, DP > 100, SP > 165). Cocaine dosing order was systematically varied among participants, with the exception that, to assure participant safety, the highest cocaine dose was never given during the first session. In order to assess the possibility that cocaine would have prolonged cardiovascular effects, 22-h recordings of ECG (i.e., Holter monitoring) were accomplished four times for each participant (following the 0 and 32 mg/70 kg cocaine dose under each maintenance condition).

Subjective-effects battery

A computerized subjective-effects battery, which was completed prior to the first cocaine dose (baseline), 4-min after each option was delivered, and 30 min after the last option of the session, was comprised of a series of 100-mm visual analog scales (VAS) labeled "Not at all" (0 mm) at one end and "Extremely" (100 mm) at the other end. Eighteen of these VAS were labeled "Stimulated," "High," "Anxious," "Sedated," "Depressed," "Hungry," "Friendly," "Miserable," "On edge," "Alert," "Tired," "Talkative," "Self-Confident," "Social," "Irritable," "Confused," "Good Drug Effect," and "Bad Drug Effect." Four VAS were used to operationalize drug craving and were labeled "I want..." "Cocaine," "Heroin," "Alcohol," and "Nicotine." Three VAS were used for ratings of dose and were labeled "Quality," "Potency," "Liking." The last VAS asked participants to indicate how much they would pay for the dose of cocaine they had just received, anchored with $0 and $25.

Performance tasks

A computerized performance battery, comprised of three separate tasks, was completed prior to the first cocaine dose, 8-min after the first cocaine dose was delivered, and 8 min after the last option of the session. The first task in the battery was a 3-min digit-symbol substitution task (DSST), which consisted of nine random three-row by three-column squares (with one square blackened per row) displayed across the top of the computer screen (McLeod et al. 1982). A randomly generated number indicated which of the nine patterns should be emulated on a keypad. Participants were required to recreate as many patterns as possible by entering the patterns associated with randomly generated numbers appearing on the bottom of the screen. The second task was a 3-min digit recall (DR) task: at the start of this task, a 7-digit number was displayed for 3 s on the computer screen. Participants were instructed to memorize the number and then to reproduce it correctly twice after the number had disappeared from the screen. They were also told that they would be asked to reproduce the number following completion of the task battery. This task was designed to assess changes in immediate and delayed recall. The third task was a 3-min repeated acquisition of response sequences task, that contained both acquisition and performance components (Kelly et al. 1993). Four buttons of the keypad were displayed on the computer screen, and participants were required to learn an eight-response sequence of button presses. When the first correct response in the sequence was emitted, a position counter incremented. The counter continued to increment each time a correct button was pressed. A points counter increased each time the entire eight-response sequence was correctly completed. Participants were instructed to earn as many points as possible during the task by repeatedly entering the correct sequence. The sequence remained the same throughout the task, but a new sequence was generated for each new task battery. After this task, participants were instructed to recognize and then recall the last 8-digit number that they had entered earlier in the DR task.

Drugs

Cocaine hydrochloride (provided by The National Institute on Drug Abuse) dissolved in sterile saline for IV injection (32 mg/ml) was prepared by the Presbyterian Hospital Manufacturing Pharmacy. Pergolide (0.05 mg tablets; Athena Neurosciences, placed in opaque 00 capsules with lactose filler) was administered at the same time each day (8:00 a.m., 8:00 p.m.). The 8:00 a.m. pergolide dose was administered 1–2 h before the first dose of cocaine. Placebo pergolide capsules contained only the lactose filler. The dose of pergolide was selected to maximize efficacy while minimizing side-effects (Malcolm et al. 1991, 1994); given pergolide's approximate half-life of 24 h, we included a 4-day wash-out period between the last pergolide administration and cocaine self-administration under the placebo maintenance condition. Doses of cocaine were administered IV over a 30-s period (5 ml saline followed by 3 ml drug, and 5 ml saline). Pergolide dose was administered under double-blind conditions, while only participants were blind to the dose of cocaine administered.

Data analysis

Repeated measures analyses of variance (ANOVA) with planned comparisons (Keppel 1991), having one between-group factor (sex)

and two within-group factors [cocaine dose (0, 8, 16, 32 mg/70 kg), pergolide dose (0, 0.05)], were used to compare the following: (1) the maximal completed ratio attained responding to receive cocaine within a session, (2) baseline (prior to the first sample dose) subjective effects, cardiovascular (HR, SP, DP), and performance measures, (3) effects of the first dose of cocaine on subjective effects, cardiovascular, and performance measures, and (4) effects of repeated cocaine doses on subjective effects, cardiovascular, and performance measures; for this analysis, time was considered an additional within-group factor. There were four planned comparisons completed for each measure: pergolide versus placebo at each dose of cocaine. If the interaction between sex and medication was significant, the comparisons between pergolide and placebo were made separately for men and women. All significant planned comparisons are reported, as well as interactions between sex and cocaine. For all measures, a 0.05 significance level was used with Huynh-Feldt corrections when appropriate.

Results

Self-administration

Figure 1 shows the maximal completed ratio attained for cocaine self-administration as a function of maintenance condition. Neither pergolide nor the participant's sex significantly influenced the maximal ratio completed per session.

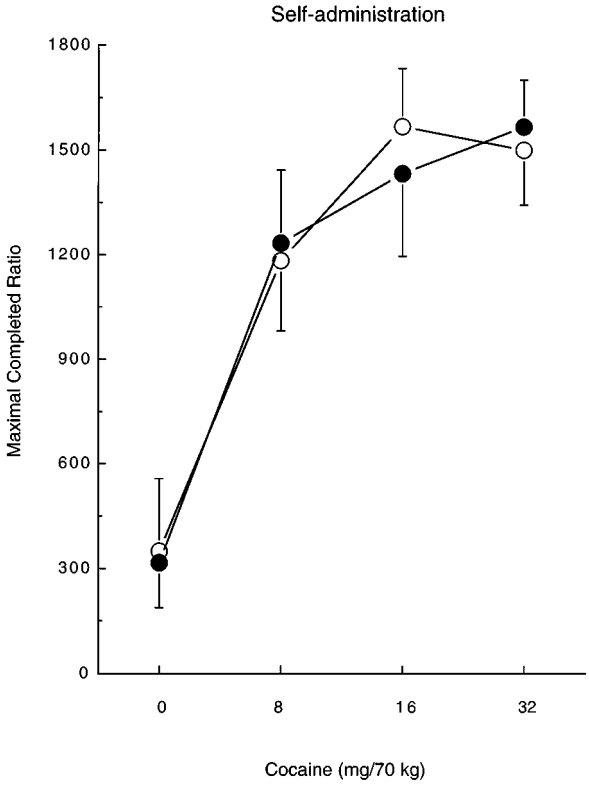

Fig. 1 Mean maximal completed ratio obtained during cocaine self-administration sessions as a function of cocaine dose and maintenance condition (maximal FR = 2200). Error bars represent ± standard error of the mean (SEM). ● Pergolide, ❍ placebo

Subjective effects measures

Baseline

There were no differences in baseline subjective-effects ratings as a function of sex or pergolide dose, except for ratings of "Miserable" [Sex × Maintenance: $F(1, 10) = 4.03$, $P < 0.01$]; pergolide increased baseline ratings of "Miserable" by an average of 10 mm for men but not women (data not shown).

Single cocaine doses

Figure 2 portrays the effects of maintenance condition on selected subjective-effects ratings as a function of cocaine dose. Pergolide significantly decreased the

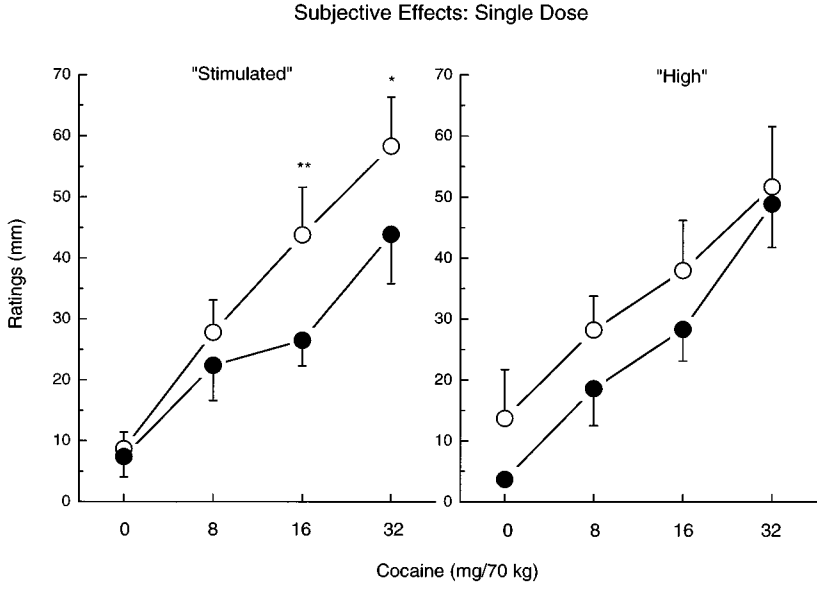

Fig. 2 Mean subjective-effects ratings as a function of cocaine dose and maintenance condition (maximal rating = 100 mm). Ratings were completed 4 min after a single cocaine dose. Error bars represent ± standard error of the mean (SEM). *Asterisks* denote a significant difference from the placebo maintenance condition at each dose of cocaine (*$P < 0.05$, **$P < 0.01$). ❍ Placebo, ● pergolide

effects of cocaine on ratings of "Stimulated" and "High" [Maintenance: $F(1,10) = 5.64$, $P < 0.04$]. By contrast, pergolide increased ratings "I Want Alcohol" [16 mg: $F(1,30) = 14.96$, $P < 0.0005$], "Irritable" [0 mg: $F(1,30) = 4.43$, $P < 0.05$], "Anxious" [16 mg: $F(1,30) = 4.13$, $P < 0.05$] and "Talkative" [Maintenance: $F(1, 10) = 6.42$, $P < 0.03$] (data not shown). There was a significant interaction between pergolide and sex for ratings of "Miserable:" [$F(1,10) = 8.84$, $P < 0.01$]. At the highest cocaine dose, pergolide decreased ratings of "Miserable" in women [$F(1,12) = 6.90$, $P < 0.02$] but not men.

Repeated cocaine doses

Figures 3 and 4 and Table 1 present self-reported effects, averaged over the session, as a function of pergolide and repeated cocaine administration ($df = 1,180$). Pergolide decreased the effects of cocaine on ratings of dose potency and how much participants liked and would pay for the cocaine dose (Fig. 3). Similarly, pergolide decreased ratings of "Good drug effect" [$F = 10.53$, $P < 0.01$], "High" [$F = 6.81$, $P < 0.02$] and "Stimulated" [$F = 11.35$, $P < 0.008$] at the 16 mg/kg dose of cocaine (data not shown).

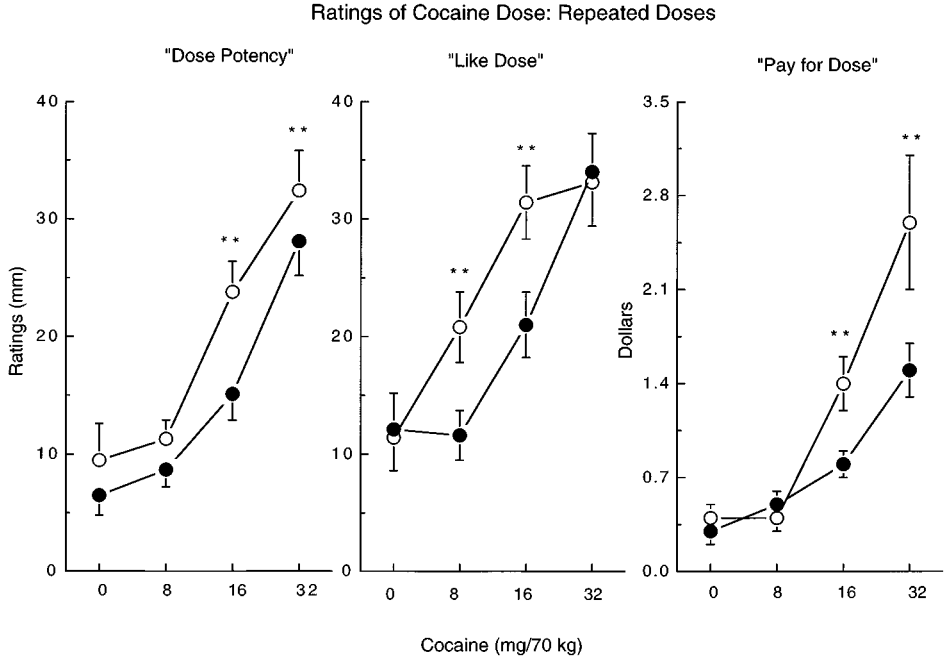

Fig. 3 Mean ratings of dose as a function of cocaine dose and maintenance condition. Ratings completed 4 min after each cocaine administration were averaged. See Fig. 2 for details. ❍ Placebo, ● pergolide

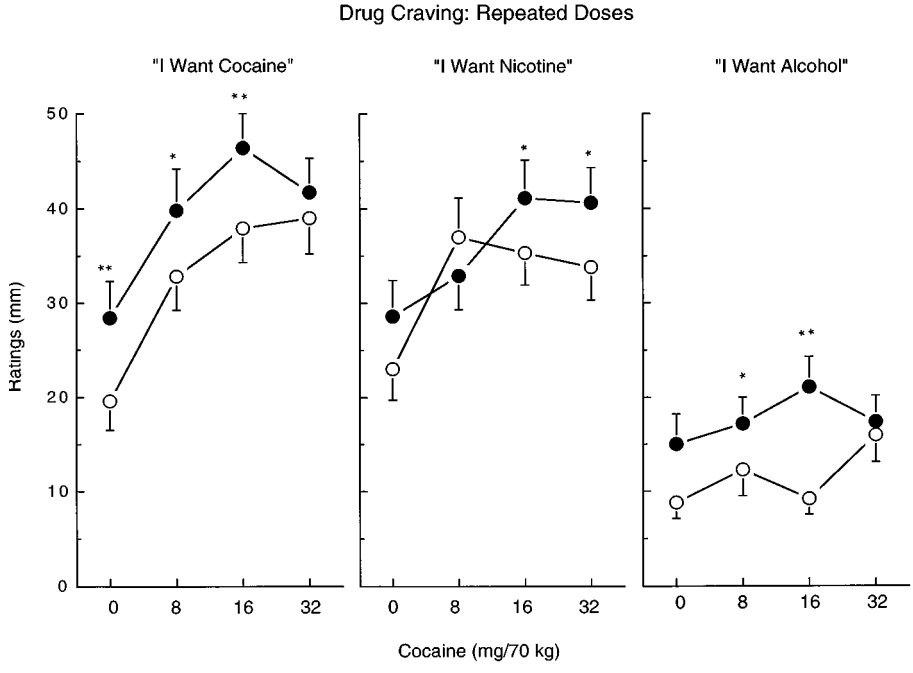

Fig. 4 Mean ratings of drug "craving" as a function of cocaine dose and maintenance condition. Ratings completed 4 min after each cocaine administration were averaged. See Fig. 2 for details. ❍ Placebo, ● pergolide

Table 1 Means (±SEM) of subjective-effects ratings following repeated cocaine administration

Cocaine dose	0 mg	8 mg	16 mg	32 mg
"Alert"				
Placebo	69.6 (3.3)	72.3 (2.9)	74.7 (2.6)	69.2 (2.9)
Pergolide	76.9 (2.8)**	78.8 (2.6)**	80.4 (2.2)*	76.7 (2.7)**
	$F = 13.2$	$F = 12.4$	$F = 9.3$	$F = 13.2$
"Friendly"				
Placebo	68.8 (3.2)	67.1 (3.3)	65.3 (3.2)	59.8 (3.4)
Pergolide	70.4 (2.9)	74.5 (2.6)***	77.3 (2.4)***	72.0 (2.6)***
		$F = 14.9$	$F = 33.1$	$F = 22.7$
"Talkative"				
Placebo	44.3 (3.6)	44.0 (3.6)	44.5 (3.4)	38.3 (3.4)
Pergolide	46.9 (3.6)	46.4 (3.6)	54.9 (3.3)***	44.2 (3.4)*
			$F = 25.8$	$F = 6.2$
"Self-confident"				
Placebo	70.3 (3.1)	69.7 (3.3)	72.8 (2.9)	64.5 (3.4)
Pergolide	81.2 (2.4)***	81.1 (2.4)***	82.1 (2.3)***	75.0 (2.9)***
	$F = 44.7$	$F = 53.5$	$F = 33.2$	$F = 31.2$
"Anxious"				
Placebo	9.2 (1.5)	15.5 (2.2)	22.4 (3.3)	25.8 (2.8)
Pergolide	18.0 (2.9)***	27.1 (3.3)***	28.6 (3.2)***	27.9 (3.4)
	$F = 23.9$	$F = 31.2$	$F = 14.4$	
"On Edge"				
Placebo	68.4 (3.6)	69.9 (3.2)	69.8 (3.5)	69.8 (2.9)
Pergolide	75.3 (2.6)**	77.0 (2.6)***	78.3 (2.3)***	72.6 (2.8)
	$F = 11.7$	$F = 18.5$	$F = 19.8$	
"Miserable"				
Placebo	71.2 (3.9)	70.4 (3.3)	65.2 (3.7)	66.8 (3.1)
Pergolide	77.0 (2.6)	73.9 (2.8)	73.0 (2.8)*	67.7 (3.3)
			$F = 8.6$	
"Tired"				
Placebo	33.6 (4.0)	24.0 (3.4)	22.9 (3.4)	25.4 (3.5)
Pergolide	41.1 (4.0)*	20.4 (3.0)	16.0 (2.5)	16.7 (2.6)*
	$F = 8.6$			$F = 7.3$

Ratings (mm) are averaged across session. F values (1,180) are presented when differences between placebo and pergolide were significant at that dose; *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$

As shown in Fig. 4, ratings of drug craving, e.g. "I Want Cocaine," "I Want Alcohol" and "I Want Nicotine" were significantly increased by pergolide. Pergolide also increased ratings of a range of moods: "Alert," "Friendly," "Talkative," "Self-confident," "Anxious," "On Edge" and "Miserable;" at the lower cocaine doses, pergolide increased ratings of "Tired" while decreasing these ratings at the highest cocaine dose (Table 1). For ratings of "Irritable," there was a significant interaction between sex and maintenance condition [$F(1,10) = 9.78$, $P < 0.01$]; pergolide decreased these ratings in men [16 mg: [$F(1,18) = 7.08$; 32 mg: $F = 16.34$, $P < 0.05$], and increased them in women [0 mg: $F = 86.6$; 8 mg: $F = 43.5$; 16 mg: $F = 20.48$, $P < 0.001$] (data not shown).

Figure 5 portrays near significant sex differences in ratings of "Stimulated" and dose quality; data are pooled across maintenance conditions. Compared to women, men tended to have higher ratings of "Stimulated" (Sex: $P < 0.08$), and they rated the higher cocaine doses as higher quality (Sex × Cocaine dose: $P < 0.08$). Men would also pay more for the higher cocaine doses (Sex × Cocaine dose: $P < 0.08$). Further, ratings of "Self-Confident" (Sex × Cocaine dose: $P < 0.08$) and "Alert" (Sex × Cocaine dose: $P < 0.08$) decreased in men but not women at the highest cocaine dose (data not shown).

Performance measures

Baseline

Women had significantly higher baseline scores on the DSST (total correct) [$F(1,10) = 5.54$, $P < 0.05$], and the Repeated Acquisition Task (total trials) [$F(1,10) = 4.77$, $P < 0.05$] compared to men. There was also a significant interaction between maintenance condition and sex on baseline performance of the Repeated Acquisition [$F(1,10) = 7.92$, $P < 0.02$] and the Digit Recall Task (% errors) [$F(1,10) = 5.81$, $P < 0.04$], with pergolide impairing baseline performance in women but not men (data not shown).

Single cocaine doses

There were significant interactions between sex and maintenance condition on the Repeated Acquisition

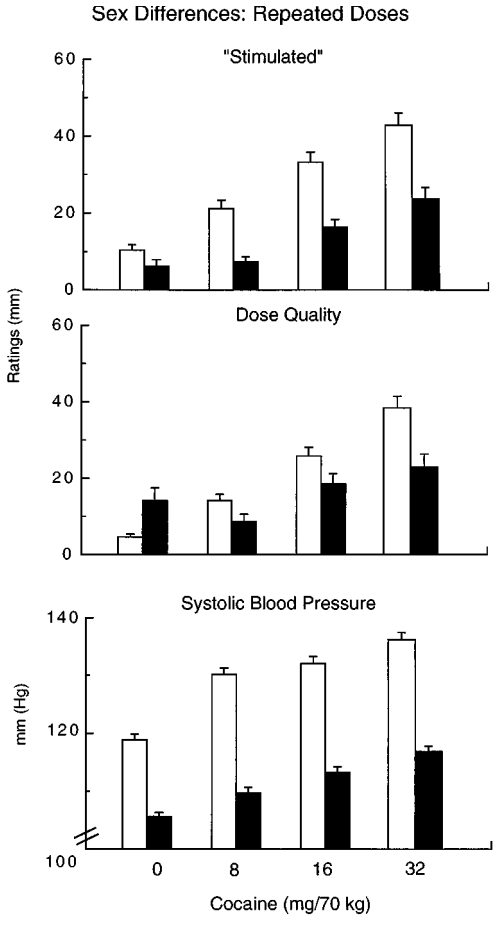

Fig. 5 Mean subjective-effects ratings and systolic blood pressure as a function of cocaine dose and sex. Ratings completed 4 min after each cocaine administration were averaged. Cardiovascular measures completed 2, 4, 6, 8, and 10 min after each cocaine administration were averaged. Data are pooled across maintenance conditions. For ratings of "Stimulated", the main effect of sex neared significance ($P < 0.08$), while for ratings of dose quality, there was a near significant interaction between sex and cocaine dose ($P < 0.08$). For systolic pressure, sex and cocaine dose significantly interacted ($P < 0.05$). See Fig. 2 for further details. *Filled bars* females, *clear bars* males

task [$F(1,10) = 6.03$, $P < 0.04$], and between sex, maintenance condition, and cocaine for the Digit Recall task [$F(3, 30) = 3.28$, $P < 0.05$]: For both tasks, pergolide impaired performance in women but not men at the 8 mg/70 kg cocaine dose [Repeated Acquisition: $F(3,30) = 11.48$; Digit Recall: $F(3,30) = 11.55$, $P < 0.02$]; at other cocaine doses, pergolide had no effect in either men or women (data not shown).

Repeated cocaine doses

Pergolide impaired performance on the Repeated Acquisition task [8 mg: $F(1,30) = 10.05$, $P < 0.03$], but did not alter cocaine's effects on any other performance measures (data not shown).

Cardiovascular measures

Baseline

There were sex differences on baseline measures of blood pressure, with women having lower systolic [$F(1,10) = 10.39$, $P < 0.009$] and diastolic ($P < 0.06$) pressure than men (data not shown).

Single cocaine doses

Pergolide significantly decreased the effects of 32 mg/70 kg cocaine on heart-rate [$F(3,30) = 5.78$, $P < 0.02$] (data not shown). Figure 6 (left panel) portrays systolic pressure as a function of cocaine dose and maintenance condition in men and women. There was a significant interaction between sex and maintenance condition on systolic blood pressure [$F = 6.08$, $P < 0.04$]. In men, pergolide enhanced the effects of the higher cocaine doses, while having no significant effect in women.

Repeated cocaine doses

The right panel of Fig. 6 portrays the effects of cocaine and pergolide on heart rate following repeated cocaine administration. Pergolide significantly attenuated the effects of 32 mg/70 kg cocaine on heart rate. There was a significant interaction between sex and cocaine dose on systolic blood pressure [$F(3,30) = 2.93$, $P < 0.05$]. As shown in Fig. 5 (bottom panel), cocaine had a significantly greater effect on systolic blood pressure in men than women; data across maintenance conditions were pooled, since there was no interaction between sex and maintenance condition following repeated administration of cocaine.

No cocaine doses were withheld in any of the 672 trials. Further, no ECG abnormalities were noted during a session or for 22 h after repeated administrations of placebo or cocaine (32 mg/kg) during either pergolide or placebo maintenance.

Plasma cholinesterase

Plasma cholinesterase, determined prior to admission, was significantly lower in women compared to men [$F(1,10) = 6.15$, $P < 0.03$]; women averaged 4.38 ± 0.4 mU/ml, compared to 6.45 ± 0.7 mU/ml in men.

Discussion

The D_1/D_2 receptor agonist, pergolide, did not significantly decrease cocaine self-administration in

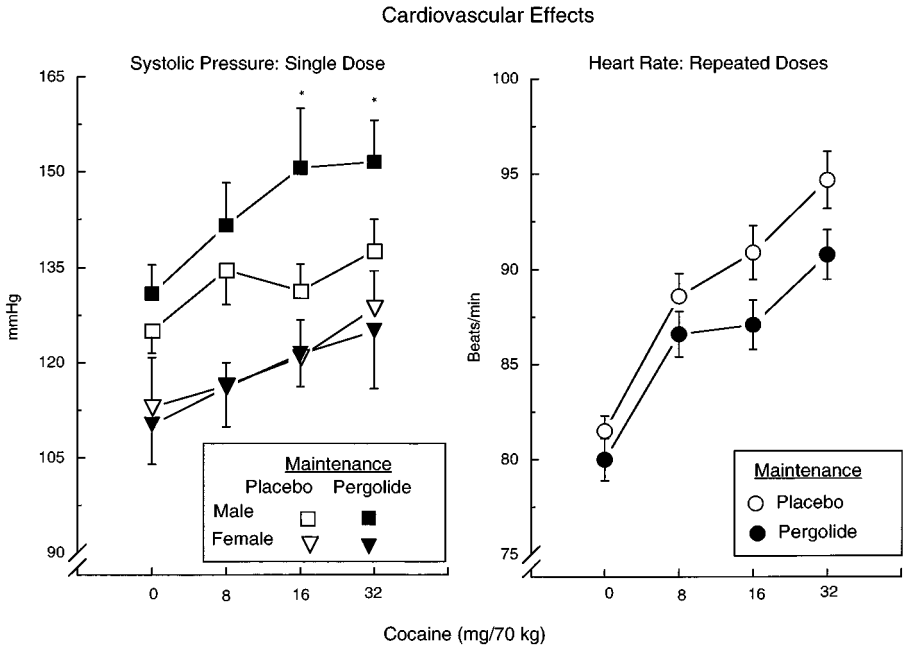

Fig. 6 Mean systolic blood pressure as a function of cocaine dose, maintenance condition and sex (*left panel*) following a single cocaine administration. Mean heart-rate as a function of cocaine dose and maintenance condition (*right panel*). Cardiovascular measures completed 2, 4, 6, 8, and 10 min after each cocaine administration were averaged. See Fig. 2 for details

either male or female cocaine abusers. However, a range of cocaine's subjective and physiological effects were decreased by pergolide, suggesting it is worthy of continued investigation as a potential treatment medication for cocaine abuse. First, pergolide attenuated some of the defining features of cocaine intoxication, e.g., increased ratings of "High," and "Stimulated" (Fischman and Foltin 1992; Woolverton and Johnson 1992), as well as the perceived potency of cocaine, and how much participants liked and would be willing to pay for the higher cocaine doses. Second, pergolide decreased the effects of single and repeated cocaine administration on heart-rate. Although pergolide also enhanced the effects of a single cocaine dose on systolic pressure in male participants, this effect did not persist with repeated cocaine doses, suggesting that pergolide decreases cocaine toxicity overall.

The rationale for investigating a dopamine agonist such as pergolide for the treatment of cocaine abuse is to identify a non-toxic compound that decreases cocaine use and is acceptable to cocaine abusers in treatment (Mello and Negus 1996). In fact, the low dose of pergolide used in the present study was well tolerated, and had stimulant-like effects in both men and women, i.e. enhancement in ratings of "Alert," "Friendly," and "Talkative," which might facilitate treatment compliance. The risks of using a dopamine agonist to treat cocaine abuse include potentiating cocaine's subjective effects, and "priming" users to self-administer cocaine (Roberts and Rinaldi 1995). Rather than potentiating cocaine's effects, pergolide attenuated ratings such as the potency and dollar value of cocaine doses. Pergolide did not increase cocaine self-administration, but did increase "craving" for cocaine, alcohol and nicotine. It is not clear why an increase in the apparent desire to use cocaine was not associated with an increase in self-administration, but we have seen a dissociation between these measures in a previous study (Fischman et al. 1990). It may be that the reported desire for cocaine did not increase sufficiently for participants to complete the demands of the modified progressive ratio schedule, in which repeatedly choosing the same option increased the behavioral requirements for obtaining that option. Nevertheless, these data suggest one risk of maintenance on this low dose of pergolide may be to increase the likelihood that abstinent cocaine users will recommence cocaine use.

It is not surprising that a stimulant would increase drug craving, as even caffeine primes cocaine self-administration in laboratory animals (Schenk et al. 1994). What is not clear is the mechanism by which pergolide attenuated cocaine's subjective effects. It may be that pergolide's effects reflect its nonselectivity as a dopamine agonist. Pergolide binds to both the D_1 and D_2 family of receptors (see Goldstein et al. 1980; Gershanik et al. 1983; Fuller and Clemens 1991), and thereby may attenuate certain of cocaine's effects by blocking dopamine from binding. There are also data to suggest that agonists at the D_1 receptor have potential utility for the treatment of cocaine abuse. Although high-efficacy D_1 agonists are self-administered by rats (Self and Stein 1992; Self et al. 1996b) and non-human primates (Weed et al. 1993; Grech et al. 1996), suggesting potential abuse liability, D_1 agonists decrease cocaine self-administration and the ability of cocaine to increase responding for more cocaine (Self et al. 1996a). By contrast, selective D_2 agonists are self-administered by laboratory animals, reinstate non-reinforced responding on a cocaine-paired lever (Woolverton et al. 1984; Wise et al. 1990; Self et al.

1996a), and appear to act additively with cocaine (see Wise 1995). More data are needed to determine if these distinctions reflect differential effects on rates of behavior or if selective D_1 agonists have potential utility for the treatment of cocaine abuse.

The second objective of this study was to determine if the effects of IV cocaine varied as a function of sex. There was a tendency for women to be less sensitive to the hypertensive and subjective effects of cocaine than men: women reported lower ratings of "Stimulated" and dose quality, and had relatively smaller increases in systolic pressure following cocaine administration. Although these findings are limited by the small number of female participants ($n = 5$), similar results have been reported in studies using intranasal (Lukas et al. 1996) and smoked cocaine (Lexau et al. 1995; Dudish et al. 1996). The relatively smaller cardiovascular effects of cocaine in women support evidence that cocaine is less toxic in females than males. In rats, cocaine's lethal dose in females is 1.8 times higher than in males (Morishima et al. 1993), and in humans, cocaine-dependent women have fewer abnormalities in cerebral perfusion than a matched sample of cocaine-dependent men (Levin et al. 1994).

This pattern does not appear to reflect differences in bioavailability, since cocaine was administered IV in the present study. Differences in the enzymatic metabolism of cocaine also seem to be an unlikely explanation: although female rats have higher levels of cholinesterase (Downs and Eddy 1932; Morishima et al. 1993), in the 12 participants used in this study, and also in a larger sample of cocaine-abusing (39F, 42M; unpublished observation) and non-drug abusing (Propert and Brackenridge 1976) volunteers, women had significantly *lower* cholinesterase levels than men. It may be that there are sex differences in the non-enzymatic hydrolysis of cocaine, which is the primary mechanism of cocaine metabolism (Isenschmid et al. 1992).

To conclude, the present data demonstrate that pergolide decreased a range of cocaine's physiological, and subjective effects, and was well tolerated by both male and female cocaine abusers. Although pergolide heightened cocaine "craving," it did not alter cocaine self-administration. These data suggest that this dose of pergolide has limited treatment utility, but that an investigation of a wider range of pergolide doses on cocaine self-administration and subjective effects is warranted.

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